UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

MJ

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/485,441	05/10/00	BALAZS L	1060-136P

002292
BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH VA 22040-0747

HM12/0507

EXAMINER	
COLEMAN, B	
ART UNIT	PAPER NUMBER
1624	9

DATE MAILED: 05/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/485,441	BALAZS et al.
Examiner	**Art Unit**
Brenda Coleman	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL.** 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 1

18)☐ Interview Summary (PTO-413) Paper No(s). _____

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

DETAILED ACTION

Claims 1-17 are pending in the application.

Specification

1. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract **on a separate sheet** is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 9-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for epilepsy, does not reasonably provide enablement for "neurodegenerative diseases". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The scope of "neurodegenerative disease" cannot be deemed enabled. The term "neurodegenerative disease" covers a broad array of different disorders that have different modes of action and different origins. The term covers such diverse disorders as Alzheimer's Disease; Parkinson's Disease; ALS and variants such as forms of ALS-PDC; Gerstmann-Straussler-Scheinker Disease (GSS); Pick's Disease; Diffuse Lewy Body Disease; Hallervordon-Spatz disease; progressive familiar myoclonic epilepsy; Corticodentatonigral degeneration;

progressive supranuclear palsy (Steele-Richardson-Olszewski); Huntington's disease; more than a dozen dementias collectively called "frontotemporal dementia and Parkinsonism linked to chromosome 17" (FTDP-17); Tourette's syndrome; Shy-Drager syndrome; Friedrich's ataxia and other spinocerebellar degenerations; Olivopontocerebellar atrophy (OPCA); spasmotic torticollis; Striatonigral degeneration; various types of torsion dystonia; certain spinal muscular atrophies, such as Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander; Hereditary spastic paraplegia, Primary lateral sclerosis; peroneal muscular atrophy (Charcot-Marie-Tooth); Creutzfeldt-Jakob Disease (CJD); Hypertrophic interstitial polyneuropathy (Dejerine-Sottas); retinitis pigmentosa; Leber's Disease; and Hypertrophic interstitial polyneuropathy. These exhibit a very broad range of effects and origins. For example, some give progressive dementia without other prominent neurological signs, such as Alzheimer's Disease, whereas other dementias have such signs, such as Diffuse Lewy Body Disease. Some give muscular wasting without sensory changes, e.g. ALS, and some do have the sensory changes such as Werdnig-Hoffmann. Some are abnormalities of posture, movement or speech, such as Striatonigral degeneration, and other are progressive ataxias, such as OPCA. Some are linked to tau mutations, such as Alzheimer's Disease and FTDP-17, and other such as Parkinson's clearly do not. Some affect only vision such as retinitis pigmentosa. Even within those that fall into the same category of effects, there are often striking differences. For example, Alzheimer's Disease and Pick's disease both give progressive dementia without other prominent neurological signs. But the characteristic Alzheimer's neurofibrillary tangles are not seen in Pick's Disease, which has straight fibrils, as opposed to the paired helical

filaments of Alzheimer's Disease. Pick's Disease gives lobal atrophy, not seen in Alzheimer's Disease. There are differences in origins, even with what little is known. Thus, among progressive dementias, CJD is definitely caused by an infectious agent; so far as can be determined, this is not so for Huntington's disease. Even among the hereditary disorders, the origins are different. Thus, FTDP-17 comes from chromosome 17, Huntington's Disease from 4, and the neurodegenerative disorder that people with Down's syndrome develop later in life is presumably connected in some way to 21.

The great majority of these have no treatment at all, and of those that do, none or virtually none have been treated with such inhibitors as are disclosed here. The great diversity of diseases falling within the "neurodegenerative disease" category means that it is contrary to medical understanding that any agent (let alone a genus of trillions of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the massive research effort on Alzheimer's Disease has produced are means of providing Acetylcholinesterase inhibition, unrelated to the mechanism of action in this case.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1-17 are vague and indefinite in that it is not known what is meant by the use of "/" in the nomenclature of the compounds of formula I, i.e. 1,3-dioxolo/**4,5-h//2,3**/benzodiazepine.

b) "Derivative" in the claims 1-17 implies more then what is positively recited. See the "derivative of formula I" and "quaternary ammonium derivatives".

c) Claims 1, 9, 16 and 17, within the definitions of R^7 and R^8 states "phthalimido group which latter is optionally substituted", however optionally substituted without reciting intended substituents renders the claim unclear and indefinite as to number and nature of substitution.

d) Claims 6 and 14 are vague and indefinite in that it is not known what is meant by "gua**m**yl".

e) Claims 6 and 14 recite the limitation "(methoxyphenoxy)-(hydroxypropyl) group" in the definitions of R^7 and R^8. There is insufficient antecedent basis for this limitation in the claim.

f) Claim 8 is vague and indefinite in that the definitions of R^3, R^4, n and m are "as defined in connection with the formula I", however, the definitions of R^3, R^4, n and m are not defined within the claim. See the process labeled c).

g) Claim 8 is vague and indefinite in that the definitions of R^7, R^8 and p are "as defined in connection with the formula I", however, the definition of R^7, R^8 and p are not defined within the claim. See the process labeled e).

h) Claim 8 is vague and indefinite in that it is not known what is meant by "and, if desired, an obtained compound".

i) Claim 8 is vague and indefinite in that the definitions of R^1, A and B are "as defined in connection with the formula I", however, the definitions of R^1, A and B are not defined within the claim.

j) "Derivative" in the claim 8 implies more then what is positively recited. See the "acylating derivative".

k) Claim 16 is vague and indefinite in that it is not known what is meant by "especially epilepsy or a neurodegenerative disease or a state after stroke". It is not known what else is being contemplated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(f) he did not himself invent the subject matter sought to be patented.

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

4. Claims 1, 5-9 and 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Hamori et al., WO 96/04283. Hamori teaches the compounds, compositions and method of use of the instant invention where A and B form a bond; R^1 is -C(=O)-NHMe, -C(=O)-OMe or -C(=O)-OEt; and R^2 is nitro or amino. See examples 28-30, 45-47, etc.

5. Claims 1-3, 5-7, 9-11 and 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Tarnawa et al., Bioorganic & Medicinal Chemistry Letters. Tarnawa teaches the compounds, compositions and method of use of the instant invention where A and B are hydrogen; R^1 is -C(=O)-NHMe, -C(=O)-NHC_4H_9, -C(=O)-NHC_6H_5, -C(=O)-CH_2NH_2, -C(=O)-CH_2NHCH_3, -C(=O)-$CH_2N(CH_3)_2$; and R^2 is amino, or "could be the same, but it was not necessarily as R^{1}", i.e. H, CH_3, C_2H_5, n-C_4H_9, $C(CH_3)_3$, etc. See examples 15-20, 23, etc.

6. Claims 1-3, 5-7, 9, 10 and 13-17 are rejected under 35 U.S.C. 102(b, f and g) as being anticipated by Andrási et al., U.S. Patent Numbers 5,639,751; 5,459,137; 5,521,174; 5,519,019; 5,604,223; and 5,536,832. Andrási teaches the compounds, compositions and method of use of the instant invention where A and B are both hydrogen; R^1 is -C(=O)-CH_2-OMe, -C(=O)-NHPh, -C(=O)-CH_2-NH_2, -C(=O)-CH_2-phthalimido, -C(=O)-NHMe, -C(=O)-CH_2-pyrrolidine, -C(=O)-

CH_2-NMe_2, -C(=O)-NHn-Bu, -C(=O)-CH_2-NHMe, -C(=O)-CH_2-NH_2, -C(=O)-CH_2Cl, etc.; and R^2 is nitro, amino or -NHC(=O)CH_3. See examples 25, 53, 70, 71, etc.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 5-9 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamori et al., WO 96/04283. The generic structure of Hamori encompasses the instantly claimed compounds (see Formula I, page 1) and by the same process (see page 7) as claimed herein. Examples 28-30 and 45-47 differ only in the nature of the R^1 and R^3 substituents. Page 3, defines the substituent R^1 as ..... nitro, ...the group -NR^8R^9, ... and R^3 as the group -C(=O)-R^{10}. Page 2, defines the substituents R^8 and R^9 as hydrogen, C_1-C_6 alkyl or the group -C(=O)-R^{13}, wherein R^{13} is C_1-C_6 alkyl and R^{10} is defined as ....the group -$NR^{11}R^{12}$, -O-C_{1-6}-alkyl,.... wherein R^{11} and R^{12} are hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted aryl. Compounds of the instant invention are generically embraced by Hamori in view of the interchange ability of the R^1 and R^3 substituents of the tricyclic ring system. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example nitro, amino or C_{1-4} alkanoylamino for instant R^2 as well as other possibilities from the generically disclosed

alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

8. Claims 1-3, 5-7, 9, 10 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrási et al., U.S. Patent Numbers 5,639,751; 5,459,137; 5,521,174; 5,519,019; 5,604,223; and 5,536,832. The generic structure of Andrási encompasses the instantly claimed compounds (see Formula I) and by the same process as claimed herein. Examples 25, 53, 70, 71, etc. differ only in the nature of the R, R^3 and R^4 substituents. Column 1, defines the substituent R as a C_{1-6} alkanoyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is benzoyl, cyclopropanecarbonyl, C_{1-5} alkylcarbamoyl or phenylcarbamoyl; R^3 is hydrogen or a C_{1-4} alkanoyl; and R^4 is hydrogen; a C_{1-6} alkanoyl group optionally substituted by a methoxy, cyano, carboxyl, amino..... Compounds of the instant invention are generically embraced by Andrási in view of the interchange ability of the R, R^3 and R^4 substituents of the tricyclic ring system. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example nitro, amino or C_{1-4} alkanoylamino for instant R^2 as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

Claim Objections

9. Claim 15 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be in the alternative. See MPEP § 608.01(n).

Conclusion

10. Applicants' attention is directed to U.S. Patent Numbers 5,639,751; 5,521,174; 5,519,019; 5,604,223; and 5,536,832, claims subject matter that is similar and/or identical to that claimed herein. Two patents cannot issue on the same subject matter, unless applicants can demonstrate that the claims are patentably distinct from the claims of this US patent, the only way to overcome this patent is by way of Interference proceedings or removal of the conflicting subject matter. See MPEP 2306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is (703) 305-1880. The examiner can normally be reached on Monday thru Friday from 9:00 AM to 5:30 PM.

The fax phone number for this Group is (703) 308-4734 for "unofficial" purposes and the actual number for **OFFICIAL** business is **308-4556**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brenda Coleman

Brenda Coleman
May 4, 2001